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10/508,957	02/03/2005	Jonathan S. Stamler	STAM3002 PCT	6780

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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,957	STAMLER ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/10/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The response filed June 10, 2008 has been received, entered and carefully considered. The response affects the instant application accordingly:

   a. Claim 75 has been amended.

   b. Claim 84 has been added.

2. Claims 75-84 are pending in the case.

3. Claims 75-84 are present for examination.

4. The text of those sections of title 35.U.S. Code not included in this action can be found in the prior Office action.

5. New grounds of rejection are set forth in the current office action.

Information Disclosure Statement

6. The information disclosure statement filed 6/10/2008 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. There is no copy of either reference presented in the IDS. It has been placed in the application file, but the information referred to therein has not been considered.

New Grounds of Rejection

7. Due to the amendment of the claims the new grounds of rejection are applied:

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 75-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims are drawn to administering dihydrolipoic acid, dithiothreitol, or tris (2-carboxyethylphosphine) to a patient no longer responsive to nitroglycerin. The disclosure teaches the administration of these compounds for patients with nitroglycerin tolerance generically but does not specifically recite and target a patient which is completely tolerant. However, disclosure does not also teach how the administration of these compounds would be any different for any patient that is any degree of nitroglycerin tolerant. The disclosure does not provide an example or specific recitations of targeting and treating that specific and narrow patient population. Nitrate tolerance is a loss of clinical sensitivity which is very broad and can be mild, moderate, severe, and many other degrees. It is noted that loss of clinical sensitivity is not complete tolerance in which a patient is not responsive at all. As taught in the art and in the disclosure (Page 1), nitrate tolerance is generally treated by increasing the dosage. Therefore, the fact pattern indicates that the artisan was not in possession of the claimed method of use.

It is noted that Applicant makes reference to Example XXXIV paragraph 207 in the publication, but the publication is misprinted where there are two Example XXXIV. The one referred to in paragraph 207 is actually Example XXXIII which is correctly printed in the instant specification.

There is also no support in the specification for the term "nitroglycerin sensitivity restoring amount" of dihydrolipoic acid, dithiothreitol, or tris (2-carboxyethylphosphine). There is no disclosure addressing what amount or range would be considered a "nitroglycerin sensitivity restoring amount". Therefore, the fact pattern indicates that the artisan was not in possession of the claimed method of use.

10. Claim 84 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of angina, an unstable coronary syndrome, it does not reasonably provide enablement for *every* condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in

the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a patient that is completely tolerant to nitroglycerin for *every* condition as no specific condition is recited for treatment. Thus, the claims taken together with the specification imply the invention is capable of addressing every condition. Additionally, the claims recite a "nitroglycerin sensitivity restoring amount" of dihydrolipoic acid, dithiothreitol, or tris (2-carboxyethylphosphine). There is no disclosure addressing what amount or range would be considered a "nitroglycerin sensitivity restoring amount". It does not allow one of skill in the art to make or use the invention.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the prior art shows that nitroglycerin is currently advised for use in angina but the benefits for conditions such as congestive heart failure have not been established to date, and are contraindicated in acute myocardial infarction, constrictive pericarditis, and pericardial tamponade (see previous Physician Desk Reference pages). As taught by Kennedy et al. (Airway response to sublingual nitroglycerin in acute asthma, JAMA), nitroglycerin was inadequate for the treatment of acute asthma and did not significantly change neither the forced expiratory volume nor the forced vital capacity of air for those tested showing that nitroglycerines in not adequate initial therapy for asthmatic attacks, in fact he

teaches that its use could be dangerous. Applicant submitted two journal abstracts: Rolla, G., et al., Pulmonary Pharmacology 1995, April - June, 8(2-3): 137-141 and Sharara, A.M., et al., Pulmonary Pharmacology and Therapeutics 11(1), 65-70 (February 1998), stating others found a benefit of nitroglycerin for asthma. The abstract by Rolla et al. is teaching the effect of nitroglycerin pretreatment for the effectiveness of the beta-agonists (e.g. salbutamol) and theophylline administered which are the treating agents in the abstract, not the nitroglycerin. The abstract by Sharara, A.M., et al. states that there is conflicting reports regarding the efficacy of GTN as a bronchodilator (second sentence of abstract). The study was on 18 patients and while bronchodilating effects were seen, the mechanism is not known, there is no indication as to why the results are different from those in Kennedy et al., especially as Sharara states that there are conflicting reports on the issue. This underscores the unpredictability of the drug for enablement for asthma and that there is no reasonable expectation for success to the degree that it is not currently recommended for treatment asthma (see previous PDR pages from 2006). The unpredictability for the drug in the art is high and it is unclear what conditions nitroglycerin would be effective, much less what the outcomes would be when combined with another drug, resulting in an unclear expectation of what would be successful, including how other drugs affect the tolerance or their potential to block nitroglycerin to affect tolerance.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance solely for the treatment of angina with nitroglycerin in Examples XXXII and XXXIII. However, the specification does not provide for all possible conditions for nitroglycerin treatment and tolerance.

(8) The quantity of experimentation necessary:
Considering the state of the art as discussed by the references above, particularly with regards to the high degree of unpredictability in the art for nitroglycerin, it is unclear what conditions nitroglycerin would be effective, much less what the outcomes would be when combined with another drug. Without experimentation, as currently claimed, the scope of the invention would require undue experimentation of one skilled in the art to address each and every condition and every combination without a clear expectation of success.

As evidenced therein, along with the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claim 84 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite as to the expression of “a nitroglycerin sensitivity restoring amount". It is unclear what the phrase is directed to. Such a phrase fails to clarify the scope that applicant seeks protection for. It does not clarify for one of skill in the art where the metes and bounds of the invention are.

For the purposes of examination, the administration of any amount of dihydrolipoic acid, dithiothreitol, or tris(2-carboxyethylphosphine) will be appropriate.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 75-78 and 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Weischer et al. (DE 4420 102 A1).

Weischer et al. teaches the use of alpha-lipoic acid, also known as dihydrolipoic acid, in combination with cardiovascular drugs, including specific embodiments for nitroglycerin (glyceryl trinitrate), for several conditions including angina and nitrate tolerance.

It is noted that the translation provided is a machine translation from the European Patent Office and for clarity "alpha Liposaure" is alpha-lipoic acid and "Glyceroltrinitrate" is nitroglycerin.

Weischer teaches the combination of alpha-lipoic acid (enantiomers, derivatives or metabolites) and organic nitrates, including nitroglycerin in combination preparation. He teaches that the combination showed a greater anti-ischemic effect than when the nitroglycerin was administered alone. Thereby the combination of nitroglycerin and other nitrates with alpha-lipoic acid/dihydrolipoic acid (dithiol) showed a therapeutic anti-organic nitrate tolerance effect (a reduction of a loss of sensitivity). There were in vitro and in vivo models performed.

The in vivo models were comprised of administering by balloon catheter to animals (dog and house pig) with follow up histological investigation. The combination is envisioned for angina pectoris, nitrate tolerance, among other conditions. Weischer teaches the composition and methods of administration for angina with humans.

The patients will inherently have some degree of tolerance as administration of nitroglycerin produces tolerance that increases over time and angina is a chronic condition (see DE 4420102, Page 6, Table 1). Administration of the combination to angina patients will inherently affect tolerance as the limiting step is administration of alpha-lipoic acid/dihydrolipoic acid (dithiol). The process of affecting the tolerance would inherently occur once administered to the patient.

It is noted that "[T]he discovery of a previously unappreciated property of a prior art composition, **or of a scientific explanation for the prior art's functioning**, does

not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342,1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

An inherent feature need not be recognized at the time of the invention. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, **but only that the subject matter is in fact inherent in the prior art reference**. The fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention.

Weischer goes on to claim the method of use in Claim 21 of nitroglycerin and other nitrates with alpha-lipoic acid/dihydrolipoic acid (dithiol) for angina pectoris, nitrate tolerance, among other conditions (citations are based on the translation provided – Specification: Page 1, paragraphs 1, 7, 9, 16-17 of 19 on page, Page 2, paragraphs 2-9 of 18 on page, Page 4, paragraph 2-10 of 28 on page, Page 6, paragraph 10-14 of 21 on page, Page 7, paragraph 14 of23 on page, Claim set: Page 2, claim 21).

All the critical elements are taught by the cited reference and thus the claims are anticipated.

Response to Arguments

15. Claims 75-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of angina, an unstable coronary syndrome, it does not reasonably provide enablement for *every* condition including every coronary syndrome, restenosis, asthma, or rectal spasm.

Applicant's arguments filed 3/24/2008 have been fully considered but they are not persuasive. Applicant asserts that the claims go to issue of nitroglycerin tolerance and the particular condition is irrelevant. This is not persuasive as the claims are to the method of administering dihydrolipoic acid, dithiothreitol, or tris(2-carboxyethylphosphine) to a patient with a condition where they are given nitroglycerin and the patient is completely tolerant. The claims as a result draw to any and every condition and are given nitroglycerin but are not responsive at all. If nitroglycerin is given to for a myocardial infarct, the patient will be completely unresponsive to the nitroglycerin and is in fact contraindicated for the condition. The disclosure does not reasonably provide enablement for *every* condition including every coronary syndrome, restenosis, asthma, or rectal spasm. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Accordingly, the rejection is maintained.

16. Claims 75-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments filed 3/24/2008 have been fully considered but they are not persuasive. Applicant's argument with respect to the support for the dosage range in paragraph 59 is not persuasive as it is directed to the non-elected invention. The argument for the reference example 4 and Figure 1 is not persuasive as it is in vitro data that does not reflect "administering inactivated mtALDH activating effective amount of agent" to a patient and a single data points for each compound is not reflective to a range for "administering inactivated mtALDH activating effective amount of agent".

Accordingly, the rejection is maintained.

17. Claims 75-78 and 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Weischer et al. (DE 4420 102 A1).

Applicant's arguments filed 3/24/2008 have been fully considered but they are not persuasive. Applicant's argument with respect to tolerance and loss of clinical sensitivity is not persuasive as tolerance and loss of clinical sensitivity are synonymous. Additionally, nitrate tolerance is broad as addressed above and encompass patients who are slightly, moderate, severely, and completely tolerant. As a result, Weischer et al. teaches the use of alpha-lipoic acid, also known as dihydrolipoic acid, in combination with cardiovascular drugs, including specific embodiments for nitroglycerin (glyceryl trinitrate), for several conditions including angina and nitrate tolerance. The in vivo models were comprised of administering by balloon catheter to animals (dog and house pig) with follow up histological investigation. The combination is envisioned for angina pectoris, nitrate tolerance, among other conditions. Weischer teaches the composition and methods of administration for angina with humans

reflected in Claim 21 which goes to the use of nitroglycerin and other nitrates with alpha-lipoic acid/dihydrolipoic acid (dithiol) for angina pectoris, nitrate tolerance, among other conditions. The arguments that claim 21 has the phrase "that organic nitrate tolerance" which Applicant asserts that words are missing is not persuasive as Applicant has not provided evidence of missing language or a translation to indicate otherwise. Additionally, the context of the phrase is the following: "Use of the combination preparations according to Requirement 1 in combination with organic nitrate requirement for the 3 for the therapy and treatment of angina pectoris, link heart insufficiency,, to the treatment of the subacute and acute kardialen pulmonary edema, the pulmonalen hypertension, ant that organic nitrate tolerance." Thereby, the claim goes to the use of the combination to treat angina pectoris, organic nitrate tolerance, pulmonary hypertension, and other listed conditions absent any evidence to the contrary. Additionally, the steps of administering the two components in a composition are taught and the resulting effects are inherent to the composition upon administration.

Accordingly, the rejection is maintained.

18. Claims 75-77, 79, and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weischer et al. (DE 4420 102 A1) in view of Prugin et al. (Interplay between Vitamin E, Glutathione and Dihydrolipoic Acid in Protection against Lipid Peroxidation).

Applicant's arguments filed 3/24/2008 have been fully considered but they are not persuasive. Applicant's argument is with respect to Weischer et al. which has been addressed above.

Accordingly, the rejection is maintained.

19. Claims 75-83 are rejected under 35 U.S.C. 103(a) as being unpatentable Weischer et al. (DE 4420 102 A1) in view of Prugin et al. (Interplay between Vitamin E, Glutathione and Dihydrolipoic Acid in Protection against Lipid Peroxidation), and in view of Getz et al. (A Comparison between the Sulfhydryl Reductants Tris(2-carboxyethyl)phosphine and Dithiothreitol for Use in Protein Biochemistry, Analytical Biochemistry).

Applicant's arguments filed 3/24/2008 have been fully considered but they are not persuasive. Applicant's argument is with respect to Weischer et al. which has been addressed above.

Accordingly, the rejection is maintained.

Conclusion

20. Claims 75-84 are rejected.

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH
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